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ARTICLES

BR96 sFv-PE40, a potent single-chain immunotoxin that selectively kills carcinoma cells

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We have constructed a single-chain immunotoxin composed of the carcinoma-reactive antibody BR96 and a truncated form of Pseudomonas exotoxin. The chimeric molecule, BR96 sFv-PE40, was expressed in Escherichia coli and localized to the inclusion bodies. We purified and identified two species of BR96 sFv-PE40, monomers and aggregates. The monomeric form was able to bind well to the BR96 antigen, a Lewisy-related antigen, while the aggregate was not. The binding affinity of the monomeric recombinant immunotoxin was 5-fold less than intact BR96 IgG, and its specificity for the BR96 antigen was confirmed by competition analysis. Monomeric BR96 sFv-PE40 was found to be extremely cytotoxic against cancer cells displaying the BR96 antigen. The cytotoxicity of the fusion protein correlates directly with antigen density on the tumor cell lines tested. The breast carcinoma cell line MCF-7, which has the highest density of BR96 antigen, was the most sensitive to BR96 sFv-PE40, with a concentration producing 50% protein synthesis inhibition of 5 pM. BR96 sFv-PE40 was found to have a t_{1/2} in serum of 28.5 min in athymic mice, compared to that of the chemical conjugate, chiBR96-LysPE40, which was 54 min. These data indicate that the single-chain immunotoxin BR96 sFv-PE40 is a potent inhibitor of protein synthesis in target cell lines and may be an effective agent for the treatment of cancer.

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